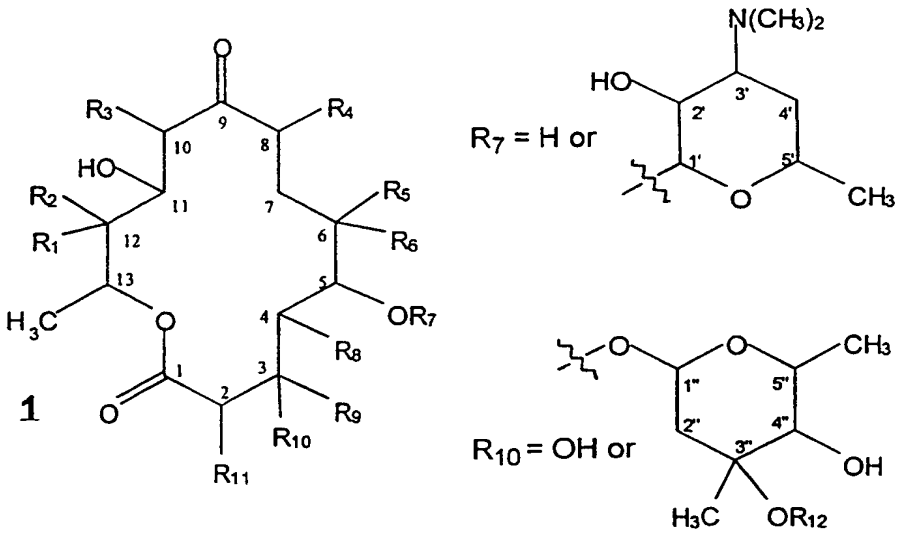
Claims

1. A 14-member macrolide which incorporates an acetate starter unit so that it has a 13-methyl substituent, with the proviso that it is not norerythromycin C, 6-deoxy-15-norerythromycin B or 6-deoxy-15-norerythromycin D.

2. 15-norerythromycin A.

3. 15-norerythromycin B.

4. A compound of the formula 1:



or a pharmaceutically acceptable salt thereof, wherein:

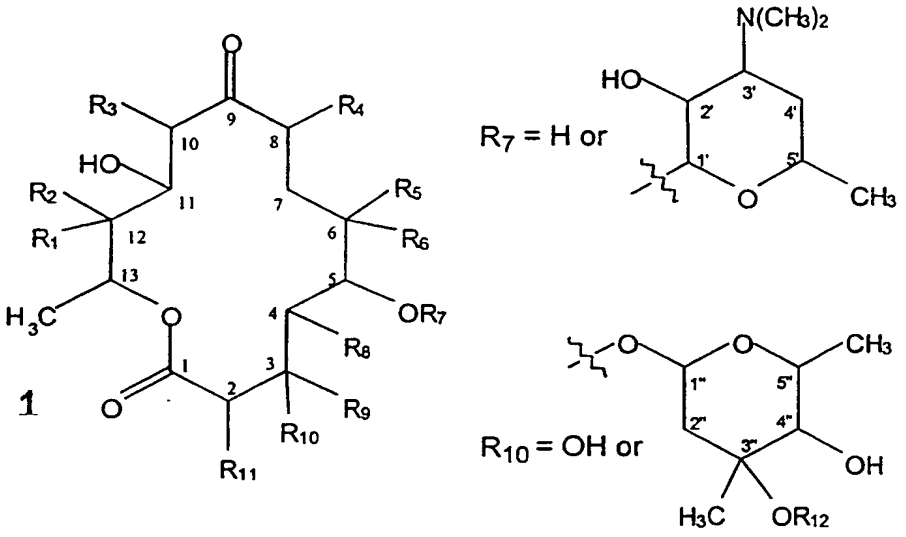
R_1 is H or OH; R_2-R_4 are each independently H, CH_3, or CH_2CH_3; R_5 is H or OH; and R_6 is H, CH_3, or CH_2CH_3; R_7 is H or desosamine; R_8 is H, CH_3, or CH_2CH_3; R_9 is OH, mycarose (R_{12} is H), or cladinose (R_{12} is CH_3), R_{10} is H; or R_9 = R_{10}

= O; and R_{11} is H, CH_3, or CH_2CH_3, with the proviso that when R_2-R_4 are CH_3, R_6 is CH_3, R_8 is CH_3, and R_{11} is CH_3, then R_1 and R_5 are not H and R_{12} is not H; or also when R_2-R_4 are CH_3, R_6 is CH_3, R_8 is CH_3, and R_{11} is CH_3, then R_1 and R_5 are not OH and R_{12} is not H.

5. A compound according to claim 4 wherein R_1 is OH; R_2-R_4 are CH_3 ; R_5 is OH; R_6 is CH_3, R_7 is desosamine; R_8 is CH_3; R_9 is cladinose (R_{12} is CH_3); and R_{11} is CH_3

6. A compound according to claim 4 wherein R_1 is H; R_2-R_4 are CH_3 ; R_5 is OH; R_6 is CH_3, R_7 is desosamine; R_8 is CH_3; R_9 is cladinose (R_{12} is CH_3); and R_{11} is CH_3.

7. A process for making compounds of the formula 1:



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wherein:

R_1 is H or OH; R_2-R_4 are each independently H, CH_3, or CH_2CH_3; R_5 is H or OH; and R_6 is H, CH_3, or CH_2CH_3; R_7 is H or desosamine; R_8 is H, CH_3, or CH_2CH_3; R_9 is OH, mycarose

(R_{12} is H), or cladinose (R_{12} is CH_3), R_{10} is H; or R_9 = R_{10} = O; and R_{11} is H, CH_3, or CH_2CH_3

8. A process for making compound of the formula <u>1</u> as set out in claim 7 wherein R_1 is OH; R_2-R_4 are CH_3 ; R_5 is OH; R_6 is CH_3, R_7 is desosamine; R_8 is CH_3; R_9 is cladinose (R_{12} is CH_3); and R_{11} is CH_3

9. A process for making compound of the formula <u>1</u> as set out in claim 7 wherein R_1 is H; R_2-R_4 are CH_3 ; R_5 is OH; R_6 is CH_3, R_7 is desosamine; R_8 is CH_3; R_9 is cladinose (R_{12} is CH_3); and R_{11} is CH_3

10. A system for producing a 14-membered macrolide incorporating an acetate starter unit, said system comprising DNA encoding and arranged to express a PKS multienzyme which comprises a loading module and a plurality of extension modules; wherein in the expressed multienzyme, said loading module is adapted to load a malonyl residue and then to effect a decarboxylation of the loaded residue to provide an acetate starter unit which is transferred to an adjacent one of said extension modules; and wherein the extension modules, or at least one thereof, are not naturally associated with a loading module that effects decarboxylation.

11. A system according to claim 10 wherein the macrolide is a compound of formula 1 as defined in any of claims 4-9.

12. A system according to claim 10 ~~or 11~~ wherein said adjacent extension module to which the acetate starter is transferred is not naturally associated with a loading module that effects decarboxylation.

13. A system according to claim 10, ~~11 or 12~~ wherein the decarboxylating functionality of the loading module is provided by a ketosynthase-type domain having a glutamine residue in the active site.

14. A system according to claim 10, ~~11 or 12~~ wherein the decarboxylating functionality of the loading module is provided by a CLF-type domain.

15. A system according to claim 14 wherein the CLF-type domain is substantially as any shown in Fig 2.

16. A system according to claim 10 ~~any of claims 10-15~~ wherein the loading module's loading functionality is provided by an acyltransferase-type domain having an arginine residue in the active site.

17. A system according to claim 10 ~~any of claims 10-16~~ wherein the loading module includes an acyl carrier protein.

18. A system according to claim 10 ~~any of claims 10-13, 16 or 17~~ wherein at least the KS_Q domain of said loading module corresponds to the loading module of the PKS multienzyme of oleandomycin, spiramycin, niddamycin, methymycin, or monensin.

~~19.~~ A PKS multienzyme as expressible by the DNA of the system of any of claims 10-18 or a variant having the ability to synthesise a compound of formula 1.

20. Nucleic acid encoding the PKS multienzyme of claim 26 ~~19.~~

21. A vector containing nucleic acid as defined in claim 20.

22. A transformant organism comprising a system according to claim 10 ~~any of claims 10-18.~~

~~23.~~ A process according to claim 7, 8, or 9 which comprises culturing an organism according to claim 22 and recovering a compound of formula 1.

24. A process according to claim ~~23~~ wherein said macrolide is a compound of formula 1 as defined in any of claims 4-9.

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25. A system, organism or process according to any of claims 10-24 wherein the plurality of extension modules corresponds to the extension modules of a PKS selected from erythromycin, narbomycin, pikromycin, lankamycin, kujimycin or megalomycin or a mutant or variant thereof able to direct synthesis of a macrolide.

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